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FABRICATION OF MICROSPONGE AS DRUG DELIVERY OF AN ANTIHYPERTENSIVE DRUG

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ABSTRACT

Microsponges are polymeric delivery systems composed of porous microspheres used for topical controlled drug delivery as well as oral controlled drug delivery system. They are small, spherical particles having a porous surface. Moreover, they can enhance stability, modify drug release favorably and reduce side effects. Microsponge technology has several favorable characteristics, which make it a versatile drug delivery system. They can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated product such as a gel, cream, liquid or powder. The outer surface is usually porous, permitting a sustained flow of substances out of the sphere. Quasi-emulsion diffusion method has been used here for the preparation of microsponges with cellulosic and acrylic polymers. Drug loading of the microsponge were estimated by UV Spectrophotometric method and was found to be within 33%- 53%. Formulations shows good buoyancy to prove it as floating microsphere. Morphology of the formulations were observed by Scanning Electron Microscopy. Almost all microsponges were found to be highly porous. Drug Release of Atenolol from prepared microsponges followed Higuchi kinetics from the formulation.

KEYWORDS: Controlled release, drug delivery, healthcare systems and Microsponges.

INTRODUCTION

There has been considerable development in novel microsponge base drug delivery systems in recent years, so as to modify and control the release behavior of the drugs. Due to having highly porous surface, microsponges are highly porous polymeric microspheres, and they look like tiny sponges. Microsponges can enhance the stability and reduce the side effect of active ingredients.[1] Polymeric base microsponges can be used for entrapment peptide, protein, DNA- based therapeutics and another wide variety of active substances, so these properties make it a versatile drug delivery vehicle. Microspheres can entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infective, anti-fungal, and anti-inflammatory agents.[2] These drug loaded microsponges can be consolidated into different formulation such as gel, cream, liquid powder, tablets. Like a true sponge, each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure, with a large porous surface. The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems, Inc. The size of the microsponges can be varied, usually from 5 – 300 µm in diameter, depending upon the degree of smoothness or after-feel required for the end formula. Although the microsponge size may vary, a typical 25 µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10ft in length, providing a total pore volume of about 1ml/g.[3] This results in a large reservoir within each microsponge, which can be loaded with up to its own weight of active agent. The microsponge particles themselves are too large to be absorbed into the skin and this adds a measure of safety to these microsponge materials. Another safety concern is the potential bacterial contamination of the materials entrapped in the microsponge. As the size of the pore diameter is smaller, the bacteria ranging from 0.007 to 0.2 µm cannot penetrate into the tunnel structure of the microsponges.[4] Microsponges show various advantages over other drug delivery systems including better controlled release of drugs than microcapsules, better chemical stability, higher payload and easier formulation.[5,6] Atenolol is a cardioselective β-adrenergic receptor blocking agent. Due to its instability problem in intestine and first pass effect, it is selected for incorporation into microsponge as a gastro retentive delivery system.[7]

MATERIALS AND METHODS

Materials

Materials required for the present work were procured from diverse sources. The drug(Atenolol) was provided as a gift sample by Windlas Biotech LTD, Dehradun,

India. Dialysis membrane was procured from Hi Media Laboratories Pvt. Ltd Mumbai, India. The other ingredients used were of analytical grade, and were used as procured.

METHODOLOGY

Preformulation study

Identification of Drug-Polymer Compatibility by FTIR

Fourier transform Infra-red (FT-IR) is the tool for solid state characterization of pharmaceutical solids. The identification of the drug was done by (FT-IR) spectroscopic method using Alpha Bruker FTIR spectrophotometer. The drug was mixed with suitable amount of KBr and converted into pellets using KBr press at 20 psi for 10 min. The disc thus prepared was placed in a sample compartment and scanned at transmission mode in the region of 4000 to 400 cm-1. The IR spectrum of the drug and drug with ethyl cellulose, polyvinyl alcohol, eudragit s100 thus obtained was compared with standard spectra of the drug.[8,9]

Formulation of micrsponges

Quasi Emulsion solvent diffusion method was employed for the formulation of microsponge. The polymer Eudragit S100 and ethyl cellulose was used in different ratios. The polymer and drug were dissolved in dichloromethane at room temperature. Then the dispersion solution was added drop-by-drop into 50 ml of 1.5% PVA aqueous solution containing 0.3% Tween 80 at room temperature. Resultant emulsion was stirred at 1000 rpm using mechanical stirrer for 2 hrs. The microsponges were separated by filtration, washed with water and dried at room temperature in a desiccator for 24hrs.[10,11]

Evaluation parameters of the prepared Microsponges

Organoleptic Properties

Color, Odour, Powder type are found by observing through naked eyes.

Bulk and tapped density, Hausner's ratio, Carr's index, Angle of repose.[12,13]

The tapped density and percent compressibility index of the micro sponges were measured by a tapping method. Angle of repose (θ) of the micro microsponges, which measures the resistance to particle flow, was determined by a fixed funnel method and all parameters are calculated using following equation.

Bulk density = Mass of Microsponges/Volume of microsponges before tapping

(1) Tapped density = Mass of Microsponges/ Volume of microsponges after tapping

(2) Hausner's ratio = Tapped density/ Bulk density

(3) Carr's index = {(Tapped density- Bulk density)/ Tapped density} X100

(4) Angle of repose (θ) = $\tan^{-1}$ (h/r)

where, h = Height of the powder cone and r = Radius of powder cone.

Determination of loading efficiency and production yield.[14,15,16]

The loading efficiency (%) of the Microsponges can be calculated according to the following equation:

Loading efficiency = {Actual Drug Content in Microsponges/ Theoretical drug content} X 100

The production yield of the Microsponges can be calculated by accurately weighing the initial weight of the raw materials and the final weight of the Microsponges obtained.

Production yield = {Practical mass of Microsponges/ Theoretical mass (polymer + drug)} X 100

Drug loading and Buoyancy Percentage

Drug-loading in microsponges was determined by dispersing 100 mg of microsponges in 50 ml ethanol or the solvent choose according to its solubility followed by agitation with a magnetic stirrer for about 30 min to dissolve the polymer and to extract the drug. After filtration through a 5µm membrane filter, the drug concentration in the ethanol phase was determined by taking the absorbance of this solution spectrophotometrically at 274nm. Eudragit S100 and drug did not interfere under these conditions. Drug concentration was then calculated. Thus, the total drug loaded in microsponges was calculated. It was expressed in percentage called as "DRUG LOADING PERCENTAGE" calculated as:

% Drug Loaded = (Actual drug content/Theoretical drug loaded) x 100.[17]

The floatation studies were carried out to ascertain the floating behavior of various polymers combinations. Beaker method was initially used to have an idea of the floatation behavior of the proposed dosage form .50 mg of floating microsphere were placed in each of four 50 ml beakers containing 20 ml of 0.1N HCl containing 0.02% tween 80. The beakers were shaken in a biological shaker at 37◦C ± 0.5◦C at 40r.p.m. Floating microspheres were collected at 4,8 and 12 hrs and dried till constant weight was obtained.[18] The percentage of floating microspheres was calculated by the following equation.

% Floating microsphere (B%) = {Weight of floating microspheres after time t/ Initial weight of floating microspheres} x 100

Particle size determination

Particle size is measured by optical microscope using optical micrometer and means particle size is used as distribution of Microsponges particles. Laser light diffractometry is used also as particle size determination. For topical use the particle size should be below 25µm, hence particles having sizes range between 10 and 25µm are preferred to use in final topical formulation.[19]

Morphology and surface topography of Microsponges

Scanning electron microscopy is used as surface morphology of Microsponges, in this method prepared Microsponges can be coated with gold platinum under an argon atmosphere at room temperature and then the surface morphology of the Microsponges can be studied by scanning electron microscopy (SEM).[20,21]

Characteristic of pore diameter & porosity

Pore volume and diameter are vital in controlling the intensity and duration of effectiveness of the active ingredient, pore size distribution, average pore diameters, total pore surface area, shape and morphology of the pores, bulk and apparent density can be determined by using mercury intrusion porosimetry and true density of micro sponges is measured using an ultra-pycnometer under helium gas.[20,21,22]

Scanning Electron Microscopy

Surface morphology of Microsponges, before drug release was visualized by scanning electron microscopy. The samples were coated with platium under vaccum pressure using Quarum and observed under various magnifications (100-1000×) with direct data capture of the images by the instrument of Varible Pressure Scanning Electron Microscopy (ZEISS EVO18, CARL ZEISS MICROSCOPY (PENTA FET X 3) OXFORDINSTRUMENTS.[23]

In Vitro Drug Release Studies

The drug release from microsponges was determined using USP paddle-type dissolution apparatus. A weighed amount of microspheres equivalent to 80 mg drug was filled into a dialysis membrane and tied with the paddle. Dissolution medium used was phosphoric acid buffer pH 1.2 and maintained at 37 ± 0.5°C at a rotation speed of 75 rpm. 5 ml of sample was withdrawn at each 1hr interval. Sample was then passed through a 5µm membrane filter, and analyzed spectrophotometrically at 274 nm to determine the concentration of drug present in the dissolution medium. The initial volume of dissolution medium was maintained by adding 5 ml of fresh dissolution media after each withdrawal. The dissolution study was continued for next 7hrs.[24,25]

RESULTS

1. Organoleptic properties, Drug Loading and Buoyancy.

Table 1: Observation table for organoleptic properties, drug loading percentage and buoyancy percentage of microsponges formed.

		Formulation A	Formulation B
Organoleptic Properties	Colour	White	White
	Odour	Odourless	Odourless
Drug Loading Percentage		33%	57%
Buoyancy Percentage		68%	87%

2. FTIR

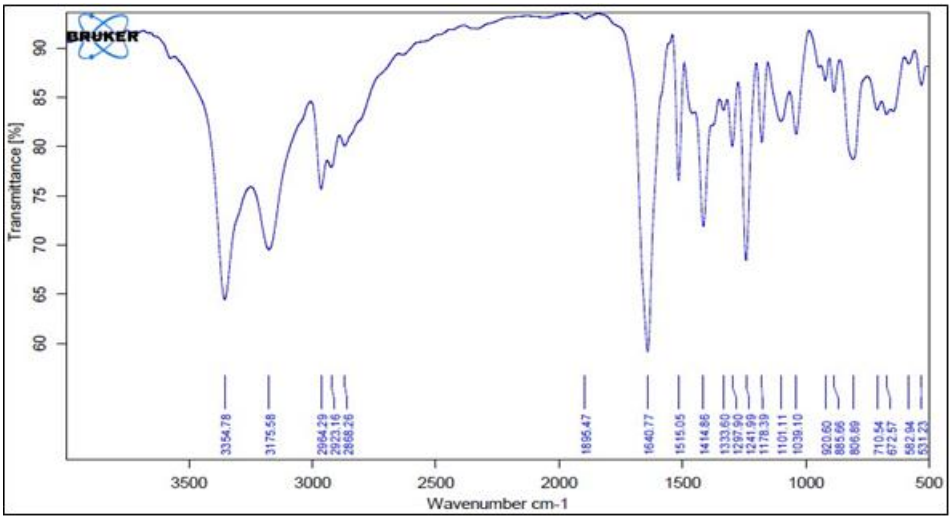

Fig 1.1: IR Spectra of Drugs.

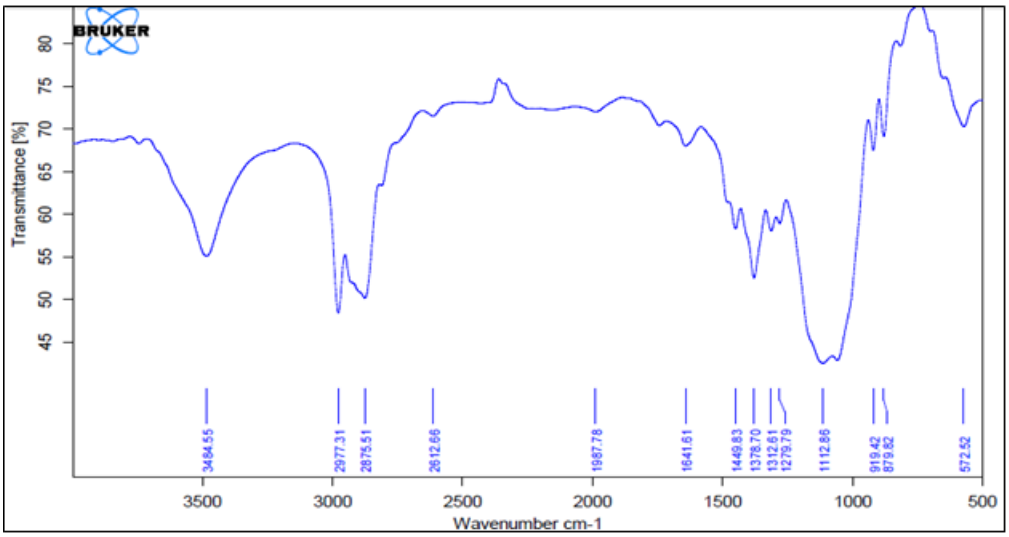

Fig 1.2: IR Spectra of Drug Polymer mixture.

3. FORMULATION

Table 2: Formulation chart of Atenolol microsponges in two types of microsponge preparation.

Sl. No.	BATCH	Formulation code	Drug (mg)	Eudragit S100 (mg)	Ethyl Cellulose (mg)
1.	A	F_1	40	-	40
2.		F_2	40	-	50
3.		F_3	40	-	60
4.	B	F_4	40	40	-
5.		F_5	40	50	-
6.		F_6	40	60	-

4. IN-VITRO DRUG RELEASE

Table 3: In-vitro drug release study from microsponge formulations A and B.

BATCH	FORMULATION /TIME (mins)	30	60	120	180	240	300	360	420
A	F_1	2.99	4.00	5.04	8.32	9.34	9.63	11.59	18.20
	F_2	1.82	3.85	6.21	10.06	21.41	26.47	26.97	30.36
	F_3	2.40	1.98	5.02	25.00	33.94	44.50	52.22	67.71
B	F_4	1.68	3.07	7.13	12.20	13.42	17.49	19.92	36.37
	F_5	2.42	5.65	8.86	13.97	15.12	19.82	34.24	46.70
	F_6	3.20	5.66	9.43	14.77	17.23	23.47	38.97	50.71

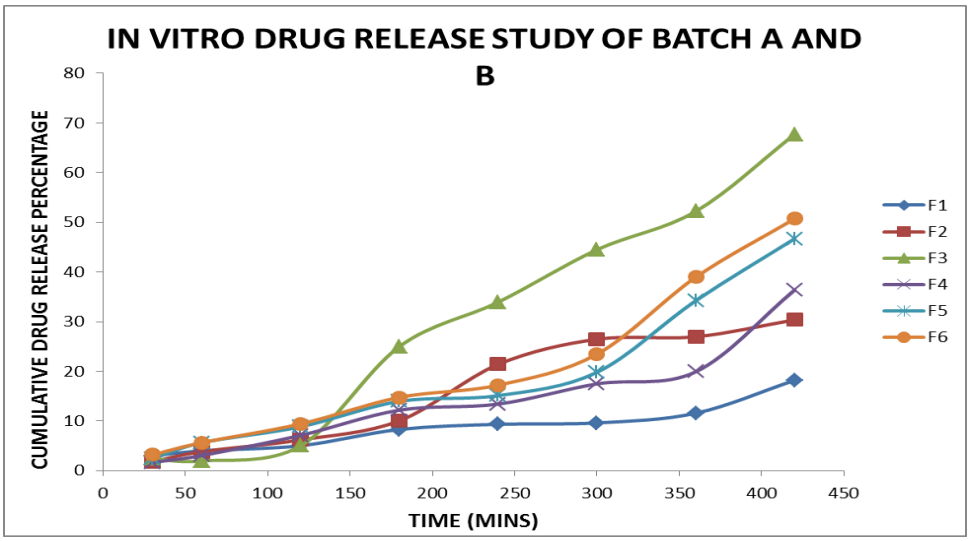

Fig 2: In vitro drug release study of batch A and B.

5. KINETIC MODELLING

RELEASE KINETICS

ZERO ORDER MODEL

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by this equation:

$Qt = Q0 + K0t$

Where Qt is the amount of drug dissolved in time t. Q0 is the initial amount of drug in the solution (most times Q0= 0. And K0 is the zero order release constant. Expressed in units of concentration/time.

To study this release kinetics data obtained from in vitro drug release studies were plotted as cumulative amount of drug release vs. time. This relationship can be described the drug dissolution of several types of modified drug release pharmaceutical dosage form as in case of the transdermal systems as well as the matrix tablets with low soluble drugs in coated forms osmotic systems etc.

HIGUCHI MODEL

The first example of a mathematical model aimed to describe drug release from a matrix system was proposed by Huguchi in 1961. Initially conceived for planar systems, it was then extended to different geometrics and porous systems This model is based on the hypotheses that initial drug concentration in the matrix is much higher than drug solubility. drug diffusion takes place only in one dimension (edge effect must be negligible). drug particles are much smaller than system thickness. matrix swelling and dissolution are negligible) drug diffusivity is constant; and perfect sink conditions are always attained in the release environment. Accordingly, model expression is given by the equation: $\mathbf{ft = Q = A\sqrt{D(2C - Cs)\,Cs\,t}}$

Where Q is the amount of drug released in time t per unit area. A, *C* is the drug initial concentration *Cs* is the drug solubility in the matrix media. D is the diffusivity of the drug molecules(diffusion constant) in the matrix substance.

This relation is valid during all the time, except when the total depletion of the drug inthe therapeutic system is achieved. To study the dissolution from a planar heterogeneous matrix system, where the drug concentration in the matrix is lower than its solubility and the release occurs through pores in the matrix.[26]

Higuchi describes the release of drugs from insoluble matrix as a square root of time dependent process based on the Fickian diffusion.

$\mathbf{Q_t = Q_0 + KHt_{1/2}}$

(where KH is the higuchi constant)

This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs.

Table 4: Kinetic Model of all the formulation.

BATCH	FORMULATION	ZERO – ORDER (r square)	HIGUCHI (r square)
A	F_1	0.9059	0.9311
	F_2	0.9526	0.8496
	F_3	0.9758	0.9244
B	F_4	0.8948	0.8288
	F_5	0.9892	0.8119
	F_6	0.9816	0.8304

6. SCANNING ELECTRON MICROSCOPY

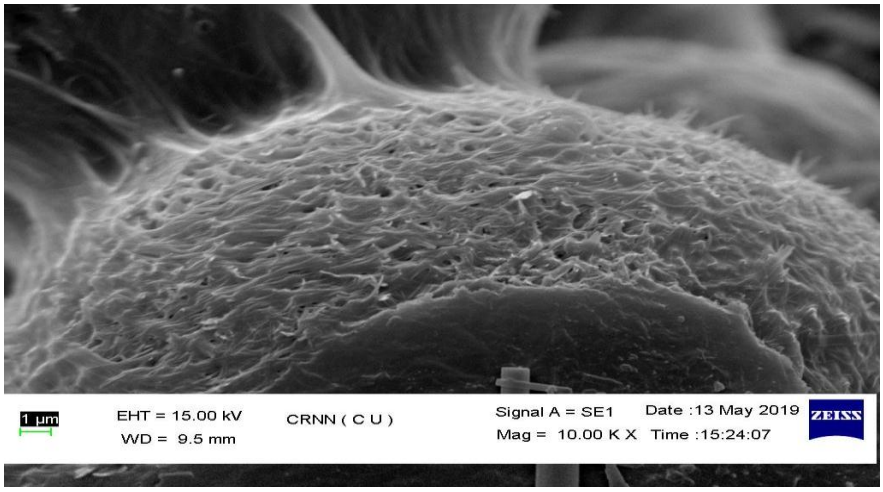

Fig 3.1: Scanning Electron Microscopic Image of Formulation.

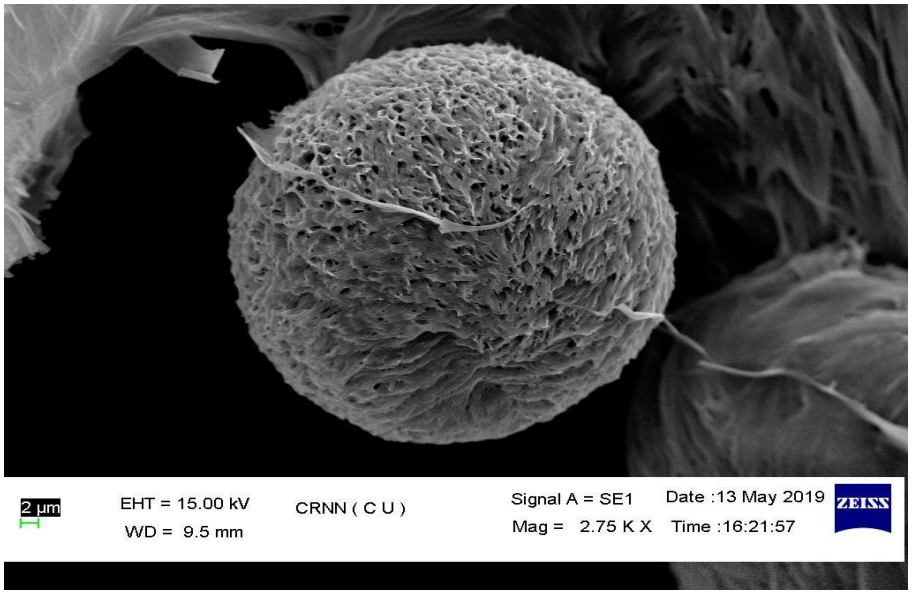

Fig 3.2: Scanning Electron Microscope Image of Formulation.

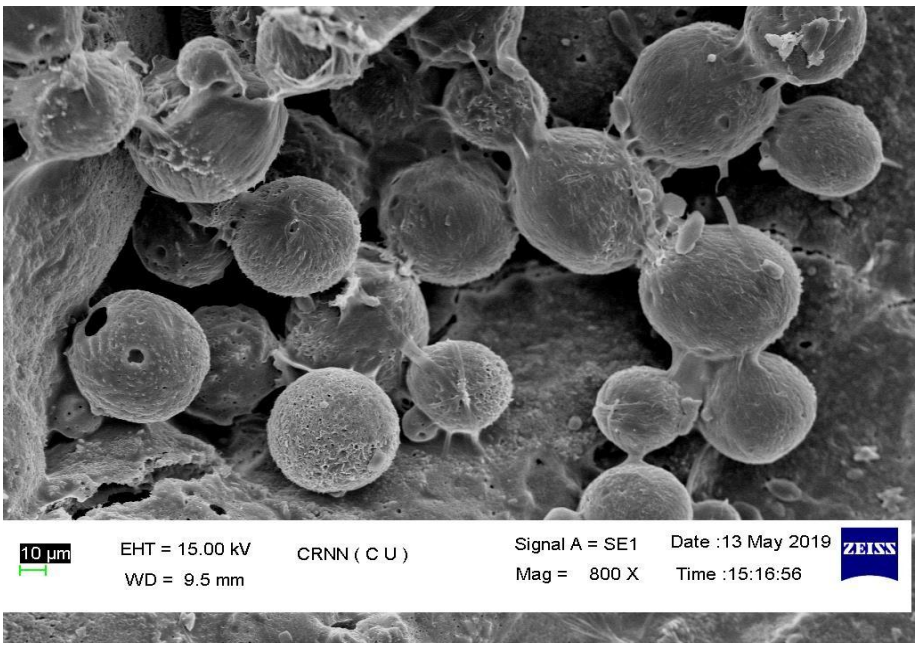

Fig 3.3: Scanning Electron Microscope Image of Formulation.

DISCUSSION

Atenolol is a β-1 selective (Cardioselective) β adrenergic receptor blocking agent. It does not have membrane stabilizing and intrinsic sympathomimetic (partial agonist) activities. Atenolol is incompletely absorbed (about 50%), but most of the absorbed dose reaches the systemic circulation. Peak blood levels are reached between two and four hours after ingestion. The elimination half-life of atenolol is 6 to 7 hours. Atenolol has no effect on plasma volume, exchangeable sodium or potassium or total body potassium. In view of first pass effect due to its instability problem in intestine, it is selected as gastro retentive delivery system.[27]

The work performed shows microsponge system as it is assumed to float in stomach with prolong release of drug. In present study Atenolol is used as the drug candidate, with Eudragit S100 as polymer. The study was carried on in different concentrations and also with two type of method of preparations such as quasi emulsion solvent diffusion technique and ionic gelation technique to get the desired cumulative release profile over a period of entire study.

All the formulations were evaluated for buoyancy lag time, drug loading and in-vitro drug release profile as well as scanning electron microscopy. Solubility study shows that mean concentration of Atenolol in phosphoric acid buffer pH 1.2 were 325 mg and 563 mg respectively. The result showed that the media is able to maintain the sink condition and suitable for drug release study.

Drug excipient interaction is a very important and prior to development of a new formulation. Among the various methodologies available to study drug-excipient interaction, Fourier Transform Infrared Spectroscopy spectrum was adopted to get the information regarding the interaction between the molecules of the level of functional groups. Figure 1.1, 1.2 indicate that the IR spectra of drug, polymer and drug-polymer combinations and polymeric combinations respectively. FTIR spectrum of procured Atenolol gives characteristic IR absorption peaks of Atenolol at 3200-3550 cm^{-1} (-OH bond), 1630 – 1500 cm^{-1}(-CH_2 bond), 1040-1100 cm^{-1}, (-C=O bond), 3198-3071 cm^{-1}(H-N bond), 2850-3000 cm^{-1}(-C-CH3 bond). FTIR study of drug-excipient mixture did not show any major shift of peaks which suggests there is no major interaction between drug and excipient except the generation of weak hydrogen bonds.

Blend of polymer is known to change the rate of diffusion of drug molecules by changing the polymeric network, leading to the change of diffusion pathways.[28] Thus the interaction might be helpful in sustaining the release of drug molecules from the experimental formulations. Prepared formulations were found to be white, tasteless product.

Drug loading of the microsponge where estimated by UV Spectrophotometric method and was found to be within 33%- 53%. Formulations shows buoyancy ability, hence can be said as floating microsponge.

Morphology of the formulations were observed by Scanning Electron Microscopy (Variable Pressure SEM). Some SEM micrographs are shown in Fig 3.1, 3.2, 3.3. The uniformly spherical shaped microsponge were visualized at (X100 -X1000). higher magnification revealed the pores formation on its surface. Almost all microsponges were found to be highly porous.

Two batches were differentiated on basis of methods in which ionic gelation techniques is superior than the quasi emulsion solvent diffusion technique if we consider drug loading.

Release of Atenolol from prepared microsponges where studied. Table 3 and figure 2 show release of Atenolol from Microsponge as described by in-vitro dissolution date, while kinetic modelling is shown in Table 4.

In batch A, formulation F_1 follows Higuchi kinetics for drug release while the other two formulations show zero order kinetics. [26] In batch B, all three formulations follow zero order kinetics.

Conflict of Interest statement

The authors report no conflicts of interest. The authors are responsible for the content and writing of this article.

Author contributions

Corresponding as well as the co-authors have contributed for research work and editing the manuscript.

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